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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Between October 1, 1991 and September 30, 1992, progress was made in four areas. First, the capabilities of SNNAP, a general purpose Simulator for Neural Networks and Action Potentials, were enhanced by incorporating mathematical descriptions of intracellular levels of Ca^{2+} and second messenger systems, which in turn modulate membrane conductances. Second, cellular mechanisms underlying operant conditioning were investigated in simulations of neural networks with biologically realistic properties. In one neural network, a learning rule (activity-dependent neuromodulation), which has been proposed as a cellular mechanism for classical conditioning, was demonstrated to support many features of operant conditioning. A second neural network was developed that simulates the biophysical properties of the neurons and synaptic interactions in a central pattern generator (CPG) underlying aspects of feeding behavior — a behavior that can be modified by operant conditioning. Third, experiments characterized the modulatory actions of transmitters on the synaptic connections and the intrinsic biophysical properties of neurons in the feeding CPG. Fourth, extensions were made to the single-cell model of associative learning by incorporating quantitative descriptions of the modulation of membrane currents by 5-HT.												
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Annual Technical Report

Grant Number: AFOSR-91-0027

Grant Title: Analysis and Synthesis of Adaptive Neural Elements and Assemblies

Period of Report: 1 October, 1991 to 30 September, 1992

I. Summary

The overall objectives of this research are to analyze the properties of identified neurons and neural networks in *Aplysia* and to examine the role of neuronal plasticity in learning and memory. Two interrelated approaches were used, one empirical and the other modeling. Between October 1, 1991 and September 30, 1992, progress was made in four areas. First, the capabilities of SNNAP, a general-purpose Simulator for Neural Networks and Action Potentials, were enhanced by incorporating mathematical descriptions of intracellular levels of Ca^{2+} and second messenger systems, which in turn modulate membrane conductances. Second, cellular mechanisms underlying operant conditioning were investigated in simulations of neural networks with biologically realistic properties. In one neural network, a learning rule (activity-dependent neuromodulation), which has been proposed as a cellular mechanism for classical conditioning, was demonstrated to support many features of operant conditioning. A second neural network was developed that simulates the biophysical properties of the neurons and synaptic interactions in a central pattern generator (CPG) underlying aspects of feeding behavior -- a behavior that can be modified by operant conditioning. Third, experiments characterized the modulatory actions of transmitters on the synaptic connections and the intrinsic biophysical properties of neurons in the feeding CPG. Fourth, extensions were made to the single-cell model of associative learning by incorporating quantitative descriptions of the modulation of membrane currents by 5-HT.

II. Research Objectives

The research supported by AFOSR-91-0027 has seven Specific Aims: 1) to conduct a detailed Hodgkin-Huxley type analysis of the membrane currents of sensory neurons and determine how the parameters governing these membrane currents are modulated by transmitters; 2) to quantitatively analyze the biophysical properties of the modulatory interneurons; 3) to incorporate empirical data into a single-cell model of learning; 4) to examine the ability of the neural circuit that mediates the tail-withdrawal reflex to support forms of associative plasticity that are analogous to higher-order features of classical conditioning; 5) to incorporate empirical data into a neural-network model for higher-order features of classical conditioning; 6) to develop a neuronal analogue of operant conditioning using identified neurons that are components of the CPG controlling feeding behavior; and 7) to incorporate empirical data into a neural-network model for operant conditioning.

III. Status of Research (Progress Report)

A. Simulator for Neural Networks and Action Potentials (SNNAP)

As indicated in previous *Annual Technical Reports*, a general-purpose Simulator for Neural Networks and Action Potentials (SNNAP) was developed. [A preliminary report of the development of SNNAP has been presented (Ziv et al., *Soc. Neurosci. Abstr.*, 17: 125, 1991) and a comprehensive report is currently in preparation (Ziv et al., 1992).] SNNAP is easy to use and versatile, yet it is realistic and quantitative. The intrinsic voltage-dependent membrane currents of individual neurons are described as an equivalent electrical circuit with Hodgkin-Huxley type

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descriptions of voltage- and time-dependent ionic currents. The user can develop a library of "cell-parameter files" that designate individual neurons, each with a unique combination of ionic currents and intrinsic biophysical properties. SNNAP is capable of simulating a network of up to 20 fully interconnected neurons and the connections among neurons can be made by either electrical or chemical synapses. The chemical synaptic connections are capable of expressing several simple forms of plasticity, such as depression with repeated stimulation or increased release in response to presynaptic spike broadening. The user can develop a library of "global-parameter files" that designate individual networks, each with unique combinations of neurons and patterns of connectivity. SNNAP was originally developed on Intel x86 based microcomputers, and since the initial report of SNNAP (Ziv et al., *Soc. Neurosci. Abstr.*, 17: 125, 1991), copies of this x86 version of SNNAP have been distributed to several outside neuroscience laboratories.

In order to enhance the capabilities of SNNAP, mathematical descriptions of intracellular second messenger systems have been incorporated. The synthesis and decay of second messengers are modeled as simple first order processes in which the user can individually specify the rates of synthesis and decay for one or more second messenger system in each neuron (e.g., see Gingrich and Byrne, *J. Neurophysiol.*, 57: 1705-1715, 1987). At present, the synthesis of second messengers is driven by the externally controlled application of a transmitter. This feature of SNNAP can simulate experimental procedures such as a brief puff of transmitter to a single neuron at a specific time and/or the bath application of a transmitter to an entire neural circuit. The intracellular concentrations of second messengers, in turn, can be linked to the conductances underlying one or more ionic currents. Thus, SNNAP can simulate membrane currents that are modulated, either enhanced or inhibited, by one or more transmitter driven second messenger system.

In addition to transmitter controlled synthesis of second messengers, mathematical descriptions of the intracellular levels of ions, such as Ca^{2+} have been incorporated. The accumulation of an ion is driven by the voltage- and time-dependent ionic current(s) for the particular species of ion. The user can specify the rate of removal (i.e., decreased concentration due to internal buffering) for individual intracellular ionic pools. The concentrations in each ionic pool, in turn, can be linked to the conductances underlying one or more ionic currents. Thus, SNNAP can simulate membrane currents that are either enhanced (e.g., Ca^{2+} -activated K^+ currents) or inhibited (e.g., Ca^{2+} -dependent inactivation of Ca^{2+} currents) by the concentration of one or more ions.

SNNAP also has been ported from the Intel x86 based microcomputer platform to the Sun SPARCstation minicomputer platform. This port allows for faster operation, which is critical as the program becomes more sophisticated and the neural networks become more complicated. (The SPARCstation port also will allow us to distribute SNNAP to those neuroscientists who prefer to work with UNIX based systems.) In addition, SNNAP has been made easier to use by incorporating a Graphical User's Interface (GUI). In the Intel x86 version, the GUI is compatible with the Microsoft Windows environment, and in the SPARCstation version, the GUI is compatible with the MIT X11 environment.

Currently, efforts are under way to allow synaptic inputs to drive the synthesis of second messengers in a neuron. This refinement will allow modulatory neurons to be simulated as elements in neural networks. In addition, more realistic descriptions of the processes underlying transmitter release are being incorporated. This refinement will allow for the simulation of a greater variety and more dynamic forms of synaptic plasticity. The development of biologically realistic simulations is an increasingly important aspect of neuroscience research, and it is likely that SNNAP can make a major contribution to this emerging field of computational neuroscience.

B. Neural Network Simulations of Operant Conditioning

One of the fundamental problems in neurobiology is to understand events occurring within individual neurons and within networks that contribute to learning and memory. An equally important and related problem is to determine the mechanistic relationships between different forms of learning. These issues have begun to be addressed with simulations of neural networks with biologically realistic properties. In one neural network, a learning rule (activity-dependent neuromodulation), which has been proposed as a cellular mechanism for classical conditioning, was demonstrated to support many features of operant conditioning. [The details of these simulations were reported recently (Raymond et al., *Neural Networks*, 5: 789-803, 1992).] Thus, there need not be fundamentally different cellular mechanisms for the two forms of associative learning. Rather, any differences in the neural mechanisms for the two forms of learning may reside in some characteristic features of the network in which the cellular plasticity is embedded.

A second neural network is currently under development that simulates a central pattern generator (CPG) underlying aspects of feeding behavior -- a behavior that can be modified by operant conditioning. [A preliminary report of the development of this network model has been presented (Ziv et al., *Soc. Neurosci. Abstr.*, 18: 1279, 1992).] In its present state of development, the network model simulates the biophysical properties of identified neurons that are part of the CPG. In addition, the network model simulates the pattern of synaptic connectivity among the neurons of the CPG. This neural model successfully simulates a pattern of neural activity that is observed in the buccal ganglia of *Aplysia* (Susswein and Byrne, *J. Neurosci.*, 8: 2049-2061, 1988). Currently, work is underway to incorporate recent experimental data (see below) describing the modulation of the synaptic connections and intrinsic neuronal properties by transmitters that affect feeding behavior. This network model of the feeding and its modulation will be used to investigate possible cellular mechanisms of operant conditioning.

C. Modulation of a Central Pattern Generator (CPG) that Underlies Aspects of Feeding Behavior

Feeding is one of three behaviors in *Aplysia* that has been shown to be modified by operant conditioning. As a first step toward investigating the cellular mechanisms of operant conditioning, characterization of a CPG that underlies aspects of feeding behavior has begun as well as an analysis of how transmitters, which affect feeding behavior in *Aplysia*, modulate this feeding CPG. Several neurons in the buccal ganglia have been identified that are members of a CPG. Susswein and Byrne (*J. Neurosci.*, 8: 2049-2061, 1988) identified cells B31/32 and B35 on the caudal surface of the buccal ganglia, and Plummer and Kirk (*J. Neurophysiol.*, 63: 539-558, 1990) identified cells B51 and B52 on the rostral surface. Recently the pattern of synaptic connectivity among these neurons was described (Baxter and Byrne, *Soc. Neurosci. Abstr.*, 17, 1590, 1991). Experiments are continuing to identify and characterize additional neurons and synaptic connections that maybe elements of feeding CPG. In addition, experiments are characterizing modulatory actions of transmitters that affect feeding behavior. Two transmitters in particular, serotonin (5-HT) and small cardioactive peptide (SCP_b), have profound effects on the CPG: 5-HT inhibits the CPG while SCP_b excites it. The actions of these two transmitters appear to be quite complex. For example, the actions of 5-HT include: 1) increasing the excitability of some elements in the CPG (e.g., B35) while decreasing the excitability of others (e.g., B4/5, B31/32, and B33); 2) enhancing the synaptic connections between some elements in the CPG (e.g., the B35 to B4/5 connection) while inhibiting others (e.g., the B4/5 to B31/32 connection); 3) inducing subthreshold oscillations in the membrane potentials of B31/32 and B33; and 4) blocking the ability of SCP_b to elicit spontaneous patterned activity and to enhance nerve evoked patterned activity. Preliminary results indicate that two other transmitters in *Aplysia*, dopamine and FMRFamide, have only mild inhibitory actions on the CPG and do not block the actions of SCP_b. Currently, experiments are examining the effects of additional transmitters that have been

identified in the buccal ganglia (e.g., myomodulin, buccalin, and histamine). Future experiments will examine the relative contributions that activity-dependent modulation of synaptic plasticity and of intrinsic biophysical properties play in altering the activity of the CPG, which in turn may underlie changes in feeding behavior during learning.

D. Extensions to the Single-Cell Model of Associative Learning

Plasticity in the sensory neurons of *Aplysia* has been used extensively as model system in which to study the cellular and molecular mechanisms of simple forms of learning. In particular, the serotonergic modulation of transmitter release and membrane currents are important mechanisms contributing to presynaptic facilitation in sensory neurons, which in turn, is thought to be a cellular mechanism contributing to sensitization and classical conditioning. Previously, a single-cell model of associative learning was developed (Gingrich and Byrne, *J. Neurophysiol.*, 57: 1705-1715, 1987) that simulated many features of synaptic plasticity in sensory neurons. This model, however, did not include realistic descriptions of the membrane currents and their modulation by 5-HT. A quantitative analysis of the K⁺ currents in sensory neurons and of the effects of 5-HT on the parameters governing these currents has been completed recently (Baxter and Byrne, *J. Neurophysiol.*, 62: 665-679; 1989; White et al., *Soc. Neurosci. Abstr.*, 18: 714, 1992; White et al., manuscript in preparation). Currently, the single-cell model of associative learning is being extended by incorporating into it a realistic Hodgkin-Huxley type membrane model. The membrane currents in the model, as well as their modulation 5-HT, are based on data from the sensory neurons. The extended model accurately simulates the normal action potential and firing properties of sensory neurons and the effects of 5-HT on the resting membrane potential, the duration of the action potential and neuronal excitability. In addition, the model accurately simulates the various forms of synaptic plasticity observed at the sensory neuron synapses and their modulation by 5-HT. The goal is to incorporate this realistic model of a sensory neuron and its synaptic terminals into a network in order to simulate the modification of reflex circuits by simple forms of learning. [Preliminary reports of simulations of such a network have reported (White et al., *Soc. Neurosci. Abstr.*, 17: 1590, 1991; White et al., manuscript in preparation).]

IV. Publications

A. Abstracts

1. White, J.A., Baxter, D.A. and Byrne, J.H. Quantitative analysis of the modulation by serotonin of the voltage-dependent potassium current in pleural sensory neurons of *Aplysia*. *Society for Neuroscience Abstracts*, 18: 714, 1992.
2. Ziv, I., Baxter, D.A. and Byrne J.H. Network model of a central pattern generator in the buccal ganglia of *Aplysia*. *Society for Neuroscience Abstracts*, 18: 1279, 1992.

B. Articles

1. Raymond, J.L., Baxter, D.A., Buonomano, D.V. and Byrne, J.H. A learning rule based on empirically-derived activity-dependent neuromodulation supports operant conditioning in a small network. *Neural Networks*, 5: 789-803, 1992.

C. Chapters

1. Byrne, J.H., Zwartjes, R., Homayouni, R., Critz, S., and Eskin, A. Roles of second messenger pathways in neuronal plasticity and in learning and memory: insights gained from *Aplysia*. In: S. Shenolikara and A.

Nairn (Eds.) *Advances in Second Messenger and Phosphoprotein Research Volume 27* (in press). New York: Raven Press, 1992.

2. Baxter, D.A. and Byrne, J.H. Learning rules in neurobiology. In: D. Gardner (Ed.), *The Neurobiology of Neural Networks* (in press). Cambridge: MIT Press/Bradford Books, 1992.

D. Manuscripts in Preparation or Under Review

1. White, J.A., Baxter, D.A. and Byrne, J.H. Quantitative analysis of the modulation by serotonin of a voltage-dependent potassium current in tail sensory neurons of *Aplysia*. In preparation for submission to *Biophysical Journal*, 1992.
2. Canavier, C.C., Baxter, D.A., Clark, J.W. and Byrne, J.H. Simulation of action potentials, excitability, and the effects of serotonin on sensory neurons in *Aplysia*. In preparation for submission to *Journal of Neurophysiology*, 1992.
3. Ziv, I., Baxter, D.A. and Byrne, J.H. Simulator for neural networks and action potentials (SNNAP). In preparation for submission to *Journal of Neurophysiology*, 1992.
4. White, J.A., Ziv, I., Cleary, L.J. and Byrne, J.H. The role of interneurons in controlling the tail-withdrawal reflex in *Aplysia*: a network model. In preparation for submission to *Journal of Neuroscience*, 1992.

V. Professional Personnel

Baxter, Douglas A., Ph.D.

Byrne, John H., Ph.D.

Canavier, Carmen C., Ph.D.

White, John A., Ph.D.

Ziv, Israel, Ph.D.

VI. Interactions: Presentations to Professional Organizations, Special Meetings, and Invited Lectures

A. Presentations to Professional Organizations

1. 21st Annual Meeting of the Society for Neuroscience, 10 November to 15 November, 1991
 - a. Dr. Ziv presented the abstract entitled "Simulator for neural networks and action potentials (SNNAP): application to a central pattern generator" on November 11, 1991.
 - b. Dr. Baxter presented the abstract entitled "Synaptic interaction among pattern generating neurons in buccal ganglia of *Aplysia*" on November 11, 1991.
 - c. Dr. Canavier presented the abstract entitled "Simulations of action potentials, transmitter release, and plasticity of sensorimotor synapses in *Aplysia*" on November 15, 1991
 - d. Dr. White presented the abstract entitled "A network model of the tail-withdrawal circuit in *Aplysia*" on November 15, 1991.

2. Third International Congress of Neuroethology, 10 August to 14 August, 1992
 - a. Dr. Byrne presented results of AFOSR-sponsored research during a lecture entitled "Neural and Molecular Bases of Simple Forms of Learning".
3. Tenth Annual Houston Conference on Biomedical Engineering Research, 19 March to 20 March, 1992
 - a. Dr. Ziv presented the abstract entitled "SNNAP: Simulator for neural networks and action potentials" on March 20, 1992.
 - b. Dr. Canavier presented the abstract entitled "Simulation of serotonin (5-HT)- induced modulation of the sensorimotor coupling in *Aplysia*" on March 20, 1991.
 - c. Dr. White presented the abstract entitled "Analysis and simulation of amplitude-to-duration conversion in a simple reflex response in *Aplysia*" on March 20, 1991.

B. Presentations to Special Meetings

1. Dahlem Workshop, 29 September to October 5, 1991 -- Dr. Byrne presented results of AFOSR-sponsored research at the Dahlem Workshop in Berlin on "Exploring Brain Function: Models in Neuroscience".
2. Bat-Sheva Seminar, 22 November to 30 November, 1991 -- Dr. Byrne presented results of AFOSR-sponsored research at the Bat-Sheva Seminar in Jerusalem on "From Neuron to Network".
3. Cold Spring Harbor Laboratory Course, 7 August to 9 August, 1992 -- As a faculty member, Dr. Byrne presented results of AFOSR-sponsored research during a series of lectures at the Cold Spring Harbor Laboratory Course on Molecular Neurobiology.

C. Invited Lectures

1. Texas A & M University 3 March, 1992 -- Dr. Byrne presented results of AFOSR-sponsored research to the Department of Biology during an invited lecture entitled "Neural and Molecular Bases of Simple Forms of Learning".
2. University of Pennsylvania 17 March to 19 March, 1992 -- Dr. Byrne presented results of AFOSR-sponsored research during an invited lecture entitled "Neural and Molecular Bases of Simple Forms of Learning".
3. Free University of Berlin 4 September to 13 September, 1992 -- Dr. Byrne presented results of AFOSR-sponsored research during a series of invited lectures and demonstrations related to "Mathematical Models of Nervous Systems and Neural Networks".

VII. New Discoveries, Inventions or Patent Disclosures

On January 21, 1992, the Intellectual Property Committee at The University of Texas Health Science Center (UTHSC) reviewed our disclosure of the software program SNNAP and recommended that the Office of Technology Management (OTM) proceed with copyright and trademark registration. With the help of the OTM, we have distributed copies of SNNAP to seven neuroscience laboratories outside UTHSC. Similar copyright and trademark protection for the newer Intel x86 and Sun SPARCstation versions of SNNAP will be pursued and SNNAP will continue to be distributed to any researcher who requests a copy.

VIII. Additional Clarifying Information -- none